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0000865323
WPI Acc no: 1975-54311W/
2-Substd 4,5-diphenyl-thiazoles - with thrombocyte aggregation inhibiting and hypocholest
Patent Assignee: SERONO LAB INC (ISTF)

Patent Family (15 patents, 14 countries)

Patent Number	Kind	Date	Application Number	Kind	Date	Update	Type
DE 2503436	A	19750807	DE 2503436	A	19750128	197533	B
BE 825097	A	19750731				197533	E
NL 197501086	A	19750804				197533	E
SE 197501010	A	19750825				197538	E
NO 197500278	A	19750825				197539	E
DK 197500331	A	19750929				197544	E
FR 2259603	A	19751003				197547	E
JP 50121269	A	19750923				197547	E
ZA 197500494	A	19751125				197613	E
AT 197500559	A	19770315				197713	E
CH 587836	A	19770513				197727	E
GB 1490771	A	19771102				197744	E
CA 1036600	A	19780815				197835	E
IL 46476	A	19781217				197902	E
AT 197607085	A	19790215				197909	E

Priority Applications (no., kind, date): CH 19741377 A 19740131

Patent Details

Patent Number	Kind	Lan	Pgs	Draw	Filing Notes
BE 825097	A	FR			
SE 197501010	A	SV			
ZA 197500494	A	EN			
CH 587836	A	DE			
CA 1036600	A	EN			
IL 46476	A	EN			

Alerting Abstract DE A
4,5-Diphenylthiazoles of formula (I) and their salts are new: (where X is halogen or NR1R2; hydroxyalkyl, 1-4C acyl or acyloxy-1-4C-alkyl, or NR1R2 is a 5- or 6- membered heterocy

bond, but is not a single bond when X = halogen) and cpds. (I; X = NR1R2) have strong thro hypocholesterolaemic activity. Cpds. (I; X = halogen) are intermediates for (I; X = NR1R2).

Title Terms /Index Terms/Additional Words: SUBSTITUTE; THROMBOCYTE; AGGREGATI

Class Codes

International Patent Classification

IPC	Class Level	Scope	Position	Status	Version Date
A61K-031/42; C07D-277/22; C07D-295/00; C07D-413/06; C07D-417/02			Secondary		"Version 7"

File Segment: CPI
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(46)

PATENT SPECIFICATION (11) 1 490 771

1 490 771

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(33) Switzerland (CH)
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(51) INT CL² C07D 277/20; A61K 31/425
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C2C 1341 1382 1532 1562 215 220 226 227 22Y 246 250 251 255 256 25Y 271 281 282 28X 29X 29Y 305 30Y 313 31Y 322 323 32Y 339 342 34Y 351 355 360 361 366 368 36Y 456 45Y 579 591 594 601 618 620 623 625 628 62X 633 650 652 658 65X 670 680 699 776 777 77Y 790 79Y KF KK KS LE NG NM ZB ZD ZL

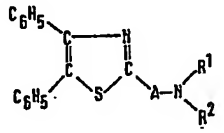
(19)

(54) 2-SUBSTITUTED 4,5-DIPHENYLTHIAZOLES AND SYNTHESIS THEREOF

(71) We, SERONO LABORATORIES INC., a Corporation organised and existing under the laws of the State of New York, United States of America, of 607, Boylston Street, Boston, State of Massachussets, 02116, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

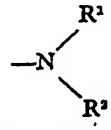
This invention relates to a series of 4,5-diphenyl-thiazole compounds substituted in the 2-position of the thiazole ring and to processes for the preparation thereof. More particularly, this invention relates to 2-(substituted)-amino- and -aminoalkyl-4,5-diphenylthiazoles having chemotherapeutic activity, as well as to intermediates therefor.

According to the present invention there is provided a compound having the formula:



(I)

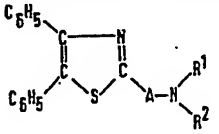
wherein X represents the radical



wherein R^1 and R^2, when considered separately, are each hydrogen, C_1—C_4 alkyl, C_1—C_4 hydroxyalkyl, C_1—C_4 acyl or acyloxyalkyl having from 1 to 4 carbon atoms in the alkyl moiety or R^1 and R^2, when taken together with the nitrogen atom to which they are attached, form a heterocyclic amino radical having 5 or 6 ring members; and A represents an alkylene group or a single bond.

One embodiment of the invention is constituted by the class of compounds of formula (I) wherein R^1 and R^2, when considered separately, are each hydrogen, C_1—C_4 alkyl, or C_1—$_4$ hydroxyalkyl or R^1 and R^2, when taken together with the nitrogen atom to which they are attached, form a heterocyclic amino radical having 5 or 6 ring members.

Another embodiment of the invention is a compound having the formula



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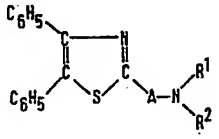
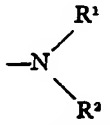
According to the present invention there is provided a compound having the formula:



(I)

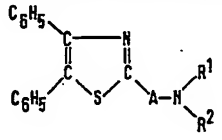
wherein X represents the radical



wherein R^1 and R^2, when considered separately, are each hydrogen, C_1—C_4 alkyl, C_1—C_4 hydroxyalkyl, C_1—C_4 acyl or acyloxyalkyl having from 1 to 4 carbon atoms in the alkyl moiety or R^1 and R^2, when taken together with the nitrogen atom to which they are attached, form a heterocyclic amino radical having 5 or 6 ring members; and A represents an alkylene group or a single bond.

One embodiment of the invention is constituted by the class of compounds of formula (I) wherein R^1 and R^2, when considered separately, are each hydrogen, C_1—C_4 alkyl, or C_{1-4} hydroxyalkyl or R^1 and R^2, when taken together with the nitrogen atom to which they are attached, form a heterocyclic amino radical having 5 or 6 ring members.

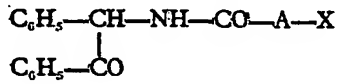
Another embodiment of the invention is a compound having the formula



wherein A is as previously defined and at least one of R^1 and R^2 is C_{1-4} acyl or acyloxyalkyl having from 1 to 4 carbon atoms in the alkyl moiety with the remaining one of R^1 and R^2, if present, being hydrogen, C_{1-4} alkyl or C_{1-4} hydroxyalkyl.

The class of compounds of this embodiment may be prepared by a process which process comprises reacting a compound of formula (I), wherein at least one of R^1 and R^2 is hydrogen or C_{1-4} hydroxyalkyl, the remaining one of R^1 and R^2, if present, being hydrogen, C_{1-4} alkyl or C_{1-4} hydroxyalkyl, with an acylating agent.

The present invention also provides a process for preparing the compounds of formula (I), wherein an α-phenylacetophenone derivative of the formula:



(II)

wherein A and X are as previously defined, is cyclized with P_2S_5 to give a compound of formula (I). The process is a single step process and uses readily available starting materials. In addition, the cyclization with P_2S_5 is straightforward and directly leads to a high yield of the desired product. The cyclization reaction may be carried out by heating the intimately mixed starting materials, decomposing any excess P_2S_5 with water or alcohol, extracting with a water — or alcohol — immiscible solvent and evaporating the solvent. A slight molar excess of P_2S_5 is preferably used.

The cyclization reaction using P_2S_5 initiates spontaneously and is exothermic. In order to avoid low yields and pitch formation, preferably the reaction mixture is quenched as soon as the cyclization reaction starts. Further operational particulars will become apparent from the specific Examples below.

The starting acetophenones may be prepared by reacting α-phenyl-α-haloacyl-amino-acetophenones with appropriate amines.

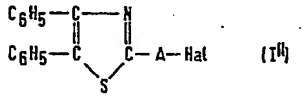
The compounds of formula (I) exhibit pharmacological activity as shown by tests on laboratory anmals. In particular, the compounds of this invention are characterized by a strong inhibitory action on platelet aggregation, often associated with a significant hypocholesterolemic activity. Antiinflammatory and analgesic activities are either low or completely absent.

Illustrative examples of the alkylene groups which may be represented by A are methylene, 1,2-ethylene, 1,3-propylene or 1,4-butylene.

Illustrative examples of the alkyl or hydroxyalkyl radical which may be represented by R^1 and R^2, when they are considered separately, are methyl, ethyl, propyl, isopropyl, hydroxymethyl or 2-hydroxyethyl.

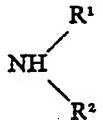
Illustrative examples of the heterocyclic amino radicals which may be represented by R^1 and R^2, when they are taken together with the nitrogen atom to which they are attached, are morpholino, pyrrolidino, piperidino or piperazino.

Compounds of formula



(I'')

wherein Hal is halogen and A is an alkylene group, may be employed in an alternative synthesis of these compounds of formula (I) wherein A is an alkylene group which is carried out by reacting a compound of formula (I'') with a compound of formula:



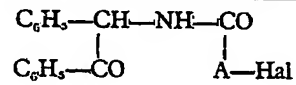
(III)

wherein R^1 and R^2 are as previously defined.

The reaction can be carried out with or without an inert solvent. Reaction times and temperatures are not critical.

The reaction products may be recovered by diluting the reaction mixture with water to precipitate the product thiazole of formula (I), extracting with a water-immiscible solvent and removing the solvent, preferably under reduced pressure.

The compounds of formula I'' may be prepared by cyclizing with P_2S_5 an α-phenylacetophenone derivative of the formula



wherein A is an alkylene group and Hal is halogen.

The compounds of formula (II) above which are used in the process of this invention as starting materials for the synthesis of compounds (I) through cyclization with P_2S_5 are conventionally prepared by reacting desylamine with an acyl halide of the formula:

$$Hal—CO—A—X$$

wherein A and X are as previously defined and Hal represents halogen.

The compounds of formula (I) wherein A represents a single bond can also be prepared by reacting a compound of formula (III) with a 2-halo-4,5-diphenylthiazole, for example, 2-chloro-4,5-diphenylthiazole or 2-bromo-4,5-diphenylthiazole.

This reaction is conventional in organic chemistry and may involve heating the starting materials for several hours, at atmospheric pressure or under elevated pressure, in a sealed tube and in the presence or in the absence of an organic solvent. An organic base, for example a tertiary amine, may be present as an acceptor of the hydrogen halide which forms during the reaction.

N-acylated derivatives of compounds of formula (I) are to be considered within the scope of the present invention. In general, N-acylation of compounds of formula (I) is carried out using the appropriate acid halide or anhydride.

Acid addition salts of the compounds (I) are also included within the scope of this invention. Pharmaceutically acceptable salts are, of course, preferred for therapeutical purposes. The hydrochlorides are preferred salts.

The invention also provides a pharmaceutical composition which comprises a compound (I) in accordance with the invention, a pharmaceutically acceptable acid addition salt thereof, or an N-acylated derivative thereof, and a pharmaceutically acceptable diluent, carrier or excipient.

The invention also includes a method for producing a hypocholesterolemic effect and/or inhibiting platelet aggregation in an animal, which method comprises administering to the animal an effective amount of a compound (I) in accordance with the invention, an acid addition salt thereof, a pharmaceutical composition in accordance with the invention, or an N-acylated derivative in accordance with the invention.

The invention will now be further described and illustrated by way of the following Examples.

The compound 2-chloro-4,5-diphenylthiazole which is used as the starting material in several of the Examples may be prepared in accordance with Acta Chem. Scand. 7(2), 374—6 (1953) by first reacting desyl chloride with potassium thiocyanate to obtain desyl thiocyanate which is then cyclized to 2-hydroxy-4,5-diphenylthiazole by means of H_2SO_4 in glacial acetic acid. The thus-obtained thiazole is treated with $POCl_3$ to give pure 2-chloro-4,5-diphenylthiazole after crystallization from 50% acetone.

EXAMPLE 1.

5.4 g. 2-chloro-4,5-diphenylthiazole and 17.4 g. morpholine were refluxed for 8 hours, whereupon the reaction mixture was cooled and diluted with water to precipitate 2-morpholino-4,5-diphenylthiazole.

The precipitate was recovered and purified by crystallization from ethanol. Yield = 4.95 g. (77%). Melting point = 116—118°C.

Analysis. Calc. for $C_{19}H_{18}ON_2S$: C = 70.78%; H = 5.62%
Found: C = 70.46%; H = 5.53%

EXAMPLE 2.

2.71 g. 2-chloro-4,5-diphenylthiazole, 10.5 g. diethanolamine and 0.5 g. powdered copper were heated to 160—170°C for 8 hours on an oil bath. After cooling, the reaction product was precipitated with water and extracted with ether. The ethereal layer was dried over NA_2SO_4 and evaporated to dryness. The oily residue was converted to a crystalline mass through addition of petroleum ether, and then recrystallized from an ethanol-ether-petroleum ether mixture.

2.5 g. 2-bis (2-hydroxyethyl)amino-4,5-diphenylthiazole (73.5%), melting at 112—113°C, were thus obtained.

Analysis. Calc. for $C_{19}H_{20}O_2N_2S$: C = 67.03%; H = 5.92%
Found: C = 67.11%; H = 5.69%

EXAMPLE 3.

10.8 g. 2-chloro-4,5-diphenylthiazole were added to a solution of 25 g. methylamine in 200 ml. benzene and heated to 120—130°C for 8 hours in a sealed vessel. After cooling, the reaction mixture was washed with water in a separatory funnel and the benzene layer was recovered, decolorized with charcoal, dried over Na_2SO_4 and evaporated to dryness to give a residue which was crystallized by means of the addition of petroleum ether.

The thus-obtained 2-methylamino-4,5-diphenylthiazole was recrystallized from an ethanol-ether-petroleum ether mixture to give 4.1 g. (38.7%) pure product melting at 177—178°C.

Analysis Calc. for $C_{16}H_{14}N_2S$: C=72.14%; H=5.29%
Found: C=72.38%; H=5.09%

EXAMPLE 4.

10.8 g. 2-chloro-4,5-diphenylthiazole, 24 g. ethanolamine and 1g. powdered copper was heated to 120—130°C on an oil bath and kept at this temperature for 5 hours. After cooling, the reaction product was precipitated with water and extracted with ether. The ethereal layer was dried ever Na_2SO_4 and evaporated to dryness. The residue was crystallized from an ethanol-ether-petroleum ether mixture to give 2-(2-hydroxyethyl)-amino-4,5-diphenylthiazole. Yield=45%. Melting point=113—115°C.

Analysis. Calc. for $C_{17}H_{16}ON_2S$: C=68.89%; H=5.44%
Found: C=68.60%; H=5.16%

EXAMPLE 5.

2.9 g. 2-(2-hydroxyethyl)amino-4,5-diphenylthiazole and 10 ml. acetic anhydride were refluxed for 6 hours. The excess reagents were distilled off and the oily residue was suspended in petroleum ether to give a crystalline mass which was recrystallized from an ethanol-ether-petroleum ether mixture. Yield=2 gr. (52.6%). Melting point=106—108°C.

The analysis confirmed that the di-acetylated derivative of the starting compound had been obtained, that is, 2-[N-acetyl-N-(2-acetoxy)ethyl]amino-4,5-diphenyl-thiazole.

Analysis. Calc. for $C_{21}H_{20}O_3N_2S$: C=66.29%; H=5.30%
Found: C=66.07%; H=5.28%

EXAMPLE 6.

The procedure described in Example 5 was repeated to prepare 2-(N-methyl-N-acetyl)amino-4,5-diphenylthiazole, starting with 2-methylamino-4,5-diphenylthiazole and acetic anhydride.

The thus-obtained monoacetylated derivative melted at 148—150°C.

Analysis. Calc. for $C_{18}H_{16}ON_2S$: C=70.10%; H=5.23%
Found: C=69.88%; H=5.52%

EXAMPLE 7.

8.13 g. 2-chloro-4,5-diphenylthiazole were added to a solution of 22 g. diethyl-amine in 100 ml. benzene and heated to 120°C for 6 hours in a sealed vessel. After cooling, the reaction mixture was washed with water in a separatory funnel, the benzene layer was recovered, dried over Na_2SO_4 and evaporated to dryness to give a residue which was dissolved in 100 ml. petroleum ether. The solution was decolorized with charcoal and cooled to give 6 g. (65%) crystalline 2-diethylamino-4,5-diphenylthia-zole, melting at 115—116°C after recrystallization from an ethanol-ether-petroleum ether mixture.

Analysis. Calc. for $C_{19}H_{20}N_2S$: C=73.98%; H=6.53%
Found: C=73.74%; H=6.22%

EXAMPLE 8.

The procedure described in Example 7 was repeated to prepare 2-isopropylamino-4,5-diphenylthiazole, starting with 2-chloro-4,5-diphenylthiazole and isopropylamine, except that the reagents were kept in a sealed vessel for 10 hours at 100°C.

The thus-obtained product melted at 116—118°C after recrystallization from aqueous ethanol.

Analysis. Calc. for $C_{15}H_{18}N_2S.H_2O$: C = 69.65%; H = 6.49%
Found: C = 69.90%; H = 6.17%

EXAMPLE 9.

5.4 g. 2-chloro-4,5-diphenylthiazole and 14.2 g. pyrrolidine were refluxed for 8 hours, whereupon the reaction mixture was cooled and diluted with water to precipitate 2-pyrrolidino-4,5-diphenylthiazole. The precipitate was recovered and purified by crystallization from aqueous ethanol. Yield = 4.9 g. (80%). Melting point = 116—117°C.

Analysis. Calc. for $C_{19}H_{18}N_2S$: C = 74.47%; H = 5.92%
Found: C = 74.21%; H = 5.70%

EXAMPLE 10.

a) α-phenyl-α-chloroacetamido-acetophenone

9.9 g. desylamine hydrochloride and 3.7 ml. chloroacetyl chloride in 100 ml. anhydrous benzene were refluxed for 4 hours in a 250 ml. flask. After filtering, the filtrate was evaporated to dryness to give 10.5 g. (88.4%) α-phenyl-α-chloroacetamido-acetophenone, melting at 117—119°C after recrystallization from aqueous ethanol.

Analysis. Calc. for $C_{16}H_{14}O_2NCl$: C = 66.78%; H = 4.90%
Found: C = 66.32%; H = 4.79%

b) α-phenyl-α-morpholinoacetamido-acetophenone

14.4 g. α-phenyl-α-chloroacetamido-acetophenone and 21.7 g. morpholine were refluxed for 4 hours, whereupon the reaction mixture was cooled and diluted with water to obtain a precipitate which was extracted with ether. The ethereal layer was evaporated to dryness and the residue was re-dissolved in 70% ethanol. After cooling to about 0°C and maintaining at this temperature for about 48 hours, crystalline α-phenyl-α-morpholinoacetamido-acetophenone was obtained. Yield = 13.2 g. (78.2%). Melting point = 116—118°C after recrystallization from aqueous ethanol.

Analysis. Calc. for $C_{20}H_{22}O_3N_2$: C = 70.98%; H = 6.55%
Found: C = 70.81%; H = 6.65%

c) 2-morpholinomethyl-4,5-diphenylthiazole hydrochloride

10 g. α-phenyl-α-morpholinoacetamido-acetophenone were intimately mixed with 6.66 g. P_2S_5, and the mixture was gradually heated to 150—170°C on an oil bath and maintained at this temperature for 1 hour. After cooling, the residue was triturated in the presence of water to completely decompose non-reacted phosphorus pentasulfide. The mixture was then made alkaline with 20% NaOH and extracted with ether. The ethereal layer was dried over Na_2SO_4, decolorized with charcoal, filtered and evaporated until dry. The residue was dissolved in ethanol and converted to the hydrochloride by means of addition of ethanolic HCl. Precipitation of 2-morpholinomethyl-4,5-diphenylthiazole hydrochloride was brought to completion by adding anhydrous ether and cooling. 4.5 g. (40.4%) product were recovered, melting at 238—242°C (dec.) after recrystallization from anhydrous ethanol.

Analysis. Calc. for $C_{20}H_{21}ON_2ClS$: C = 64.41%; H = 5.67%
Found: C = 64.29%; H = 5.77%

EXAMPLES 11 to 14.

The procedure described in Example 10 (b) was repeated to prepare the following compounds, starting with α-phenyl-α-chloro-acetamido-acetophenone and the appropriate amine:

Example (11) α-phenyl-α-pyrrolidinoacetamido-acetophenone, m.p. 142—143°C
Example (12) α-phenyl-α-piperidinoacetamido-acetophenone, m.p. 107—109°C
Example (13) α-phenyl-α-dimethylaminoacetamido-acetophenone, m.p. 119—120°C
Example (14) α-phenyl-α-isopropylaminoacetamido-acetophenone, m.p. 111—113°C

When the compounds of Examples 13 and 14 were prepared, the reaction was carried out at room temperature using benzene as the reaction medium.

EXAMPLES 15 to 18.

The procedure described in Example 10 (c) was repeated to prepare the following compounds, starting from the appropriate α-phenyl-α-aminoacetamido-acetophenone.

Example (15) 2-pyrrolidinomethyl-4,5-diphenylthiazole hydrochloride, m.p. 242—243°C

Example (16) 2-piperidinomethyl-4,5-diphenylthiazole hydrochloride, m.p. 230—235°C

Example (17) 2-isopropylaminomethyl-4,5-diphenylthiazole hydrochloride, m.p. 210—212°C

Example (18) 2-methylaminomethyl-4,5-diphenylthiazole hydrochloride, m.p. 122—124°C

Acute toxicity was determined in rats both by oral and i.p. administration after a fasting period of 16 hours. All of the test compounds were found to be non-toxic up to the doses of 300 mg/kg p.o. and 100 mg/kg i.p., respectively.

EXAMPLE 19.

a) 2-chloromethyl-4,5-diphenylthiazole

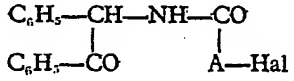
14.4 g α-phenyl-α-chloroacetamido-acetophenone were intimately mixed with 11 g. P_2S_5, and the mixture was heated to 150—170°C on an oil bath and maintained at this temperature for 1 hour. After cooling, the solid residue was triturated in the presence of a 1:1 mixture (w/w) of water and ethanol in order to completely decompose the non-reacted phosphorus pentasulfide. The mixture was further diluted with water, then made alkaline with 20% NaOH and extracted with ether. The ethereal layer was dried over Na_2SO_4, decolorized with charcoal, filtered and evaporated until dry under vacuum to give 6 g. (42% yield) of crude 2-chloromethyl-4,5-diphenylthiazole. Melting point = 46—48°C, after recrystallization from an ether-petroleum ether mixture.

b) 2-morpholinomethyl-4,5-diphenylthiazole hydrochloride

6 g 2-chloromethyl-4,5-diphenylthiazole and 9.14 g morpholine were refluxed for 4 hours, whereupon the reaction mixture was cooled and diluted with water. The oil which separated was extracted with ether and the ethereal layer was dried over Na_2SO_4 and evaporated to dryness under high vacuum. The oily residue was redissolved in the minimum amount of absolute ethanol, made acid by means of 30% ethanolic HCl and crystallized through the addition of anhydrous ether.

6.65 g crystalline 2-morpholinomethyl-4,5-diphenylthiazole hydrochloride (85% yield) were recovered by filtration. Melting point and analysis were strictly in accordance with those indicated in Example 10(c).

Examples 10 and 19 show that identical products of formula (I) can be prepared through two alternative routes, that is, (a) cyclization of a compound of formula (II) to give directly a compound of formula (I), and (b) cyclization of a compound of formula



and subsequent reaction of the thus-obtained compound of formula (I") with a compound of formula (III).

Inhibitory activity on platelet aggregation was determined *in vitro* on platelet-rich rabbit plasma prepared by collecting the blood in a plastics centrifuge tube containing enough 3.8% sodium citrate to give a concentration of 0.38 g/100 ml. when mixed with the blood, and then centrifuging at 100 *g* for 20 minutes.

1 ml. aliquots of the thus-prepared plasma were placed in a Platelet Aggregation Meter connected to a potentiometric recorder and tested according to Born, Nature (London, *194*, 927 (1962). Plasma-test compound mixtures were incubated for 10 min. at 37°C before adding the aggregating agents (ADP, collagen).

Curves were read following the method described by O'Brien et al., Thromb. Diath, Haemorrhag. *16*, 751 (1966). Slope and maximum transmission were recorded and expressed as % change with respect to controls. In the case of collagen-induced platelet aggregation, the delay time (" reaction time ") in seconds from the addition of the aggregating agent to the inflection of the curve was also measured and expressed as % change as above.

For comparison purposes, such known anti-aggregating agents as acetylsalicylic acid and adenosine were also tested in the same conditions as the test compounds.

The results are shown in the following Tables. Negative figures in slope and maxi-

mum transmission % changes indicate anti-aggregating activity; positive figures in delay time % changes indicate that the compound is effective in prolonging the "reaction time' in the collagen-induced platelet aggregation test.

TABLE 1

ADP (5 μg/ml) INDUCED PLATELET AGGREGATION

Compound of Example	Concentration μg/ml.	Max. transmission % change	Slope, % change
2	100	− 11.7	− 1.95
2	200	− 40.3	− 40.5
10 (c)	100	− 8.71	− 4.55
10 (c)	200	− 12.8	− 10.0
1	100	− 12.5	− 11.8
1	200	− 33.2	− 31.8
Adenosine	100	− 72.3	− 52.5

TABLE 2

COLLAGEN (40 μg/ml) INDUCED PLATELET AGGREGATION

Compound of Example	Concentration, μg/ml.	Max. transmission, % change	Slope, % change	Delay time ("reaction time") % change
2	5	− 82.4	− 92.2	+ 136.6
2	2.5	− 76.3	− 89.3	+ 108.2
2	1.25	− 84.3	− 97.7	+ 119.5
10 (c)	5	− 84.7	− 93.8	+ 29.8
10 (c)	2.5	− 63.0	− 80.4	− 7.14
10 (c)	1.25	− 24.9	− 23.6	+ 51.6
1	5	− 62.2	− 77.7	+ 118.5
1	2.5	− 60.8	− 74.9	+ 85.0
1	1.25	− 24.1	− 38.8	+ 16.2
Acetylsalicylic acid	5	− 61.6	− 74.2	− 49.0
,,	2.5	− 41.9	− 52.0	+ 15.5
,,	1.25	+ 6.70	+ 10.6	+ 7.3

Hypocholesterolemic activity was tested on hypercholesterolemic rats that had received the indicated daily doses of the test compounds for two days. Cholesterol was then assayed in the blood and compared to controls. The compound of Example 10(c) administered p.os at the dose of 200 mg/kg caused a 17% decrease of the cholesterol amount with respect to controls. At the same dose p.os as above, the compound of Example 2 caused a 22% decrease.

Antiinflammatory activity was tested plethysmometrically by measuring the rat-paw edema volume induced by brewer's yeast in rats to which the test compounds had been administered p.os 1 hour before the injection of the edema inducing agent. No significant reduction of edema volume was found in treated animals (100 mg/kg. p.os) when compared with controls.

Analgesic activity was tested by the hot-plate method.

An analgesic effect was not demonstrated by any of the test compounds when administered p.os at the dose of 100—200 mg/kg. The preferred way of administration of the compounds of this invention is per os. The following Example shows a typical preparation of capsules.

EXAMPLE 20.

A blend is prepared containing the following proportions of excipients expressed in parts by weight:

glycocoll	2.5
lactose	5
talc	2.5
magnesium stearate	1

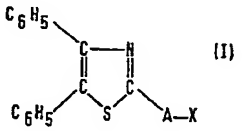
The above blend is mixed with sufficient amounts of the compounds of Examples 1, 2 and 10 (c) to give capsules containing 25,100 and 200 mg. of each of the active ingredients and filled into gelatin capsules for oral administration.

Insofar as the present invention includes a method for producing a hypocholesterolemic effect and/or inhibiting platelet aggregation in an animal, which method comprises administering to the animal an effective amount of a compound (I) in accordance with the invention, an acid addition salt thereof, a pharmaceutical composition in accordance with the invention, or an N-acylated derivative in accordance with the invention, it should be clearly understood that we make no claim herein to such a method when used in the treatment or prevention of disease in human beings.

Subject to the foregoing disclaimer:

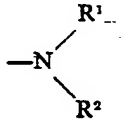
WHAT WE CLAIM IS:

1. A compound having the formula:



(I)

wherein X represents the radical



wherein R^1 and R^2, when considered separately, are each hydrogen, C_1—C_4 alkyl, C_1—C_4 hydroxyalkyl, C_1—C_4 acyl or acyloxyalkyl having from 1 to 4 carbon atoms in the alkyl moiety or R^1 and R^2, when taken together with the nitrogen atom to which they are attached, form a heterocyclic amino radical having 5 or 6 ring members; and A represents an alkylene group or a single bond.

2. A compound as claimed in claim 1, wherein R^1 and R^2, when considered separately, are each hydrogen, C_1—C_4 alkyl, or C_{1-4} hydroxyalkyl or R^1 and R^2, when taken together with the nitrogen atom to which they are attached, form a heterocyclic amino radical having 5 or 6 ring members.

3. An acid addition salt of a compound as claimed in claim 1.

4. An acid addition salt of a compound as claimed in claim 2.

5. A pharmaceutically acceptable acid addition salt of a compound as claimed in claim 1.

6. A pharmaceutically acceptable acid addition salt of a compound as claimed in claim 2.

7. A salt as claimed in claim 5 which is a hydrochloride.

8. A salt as claimed in claim 6 which is a hydrochloride.

9. An N-acylated derivative of a compound as claimed in claim 1.

10. 2-morpholino-4,5-diphenylthiazole.

11. 2-bis(2-hydroxyethyl)amino-4,5-diphenylthiazole.

12. 2-methylamino-4,5-diphenylthiazole.

13. 2-(2-hydroxyethyl)amino-4,5-diphenylthiazole.

14. 2-[N-acetyl-N-(2-acetoxy)ethyl]amino-4,5-diphenylthiazole.

15. 2-(N-methyl-N-acetyl)amino-4,5-diphenylthiazole.

16. 2-diethylamino-4,5-diphenylthiazole.

17. 2-isopropylamino-4,5-diphenylthiazole.

18. 2-pyrrolidino-4,5-diphenylthiazole.

19. 2-morpholinomethyl-4,5-diphenylthiazole hydrochloride.

20. 2-pyrrolidinomethyl-4,5-diphenylthiazole hydrochloride.

21. 2-piperidinomethyl-4,5-diphenylthiazole hydrochloride.

22. 2-isopropylaminomethyl-4,5-diphenylthiazole hydrochloride.

23. 2-methylaminomethyl-4,5-diphenylthiazole hydrochloride.

24. A compound as claimed in claim 1 or a salt as claimed in claim 3, claim 5, or claim 7, wherein A is methylene, 1,2-ethylene, 1,3-propylene or 1,4-butylene.

25. A compound as claimed in claim 2 or a salt as claimed in claim 4, claim 6, or claim 8, wherein A is methylene, 1,2-ethylene, 1,3-propylene or 1,4-butylene.

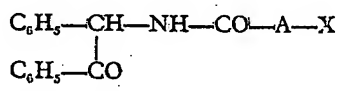
26. A compound as claimed in claim 1 or a salt as claimed in claim 3, claim 5 or claim 7, wherein R^1 and R^2, when they are considered separately, are methyl, ethyl, propyl, isopropyl, hydroxymethyl or 2-hydroxyethyl.

27. A compound as claimed in claim 2 or a salt as claimed in claim 4, claim 6 or claim 8, wherein R^1 and R^2, when they are considered separately, are methyl, ethyl, propyl, isopropyl, hydroxymethyl or 2-hydroxyethyl.

28. A compound as claimed in claim 1 or a salt as claimed in claim 3, claim 5 or claim 7, wherein R^1 and R^2, when they are taken together with the nitrogen atom to which they are attached, are morpholino, pyrrolidino, piperidino or piperazino.

29. A compound as claimed in claim 2 or a salt as claimed in claim 4, claim 6 or claim 8, wherein R^1 and R^2, when they are taken together with the nitrogen atom to which they are attached, are morpholino, pyrrolidino, piperidino or piperazino.

30. A process for preparing a compound as claimed in claim 1, which process comprises cyclizing with P_2S_5 an α-phenyl-acetophenone derivative of the formula



(II)

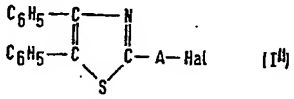
wherein A and X are as defined in claim 1.

31. A process as claimed in claim 30, wherein a slight molar excess of P_2S_5 is used.

32. A process as claimed in claim 30 or claim 31, wherein the process is carried out by heating the intimately mixed starting materials, decomposing any excess P_2S_5 with water or alcohol, extracting with a water- or alcohol-immiscible solvent and evaporating the solvent.

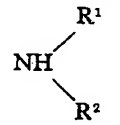
33. A process as claimed in any one of claims 30 to 32, wherein the reaction mixture is quenched as soon as the cyclization reaction starts.

34. A process for preparing a compound as claimed in claim 1 wherein A is an alkylene group, which process comprises reacting a compound of formula



(IV)

wherein A is an alkylene group and Hal is halogen, with a compound of the formula



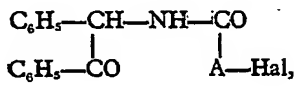
(III)

35. A process as claimed in claim 34, wherein an inert solvent is present.

36. A process as claimed in claim 34 or claim 35, wherein the compound as claimed in claim 1 is recovered by diluting the reaction mixture with water to precipitate said compound, extracting with a water-immiscible solvent and removing the solvent.

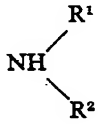
37. A process as claimed in claim 36, wherein the solvent is removed under reduced presssure.

38. A process as claimed in any one of claims 34 to 37, wherein the starting compound of formula (I″) has been prepared by cyclizing with P_2S_5 an α-phenylacetophenone derivative of the formula



wherein A and Hal are as defined in claim 34.

39. A process for preparing a compound as claimed in claim 1 wherein A is a single bond, which process comprises reacting a compound of the formula:



(III)

with a 2-halo-4,5-diphenylthiazole.

40. A process as claimed in claim 39, which process comprises heating the starting materials for several hours, at atmospheric pressure or under elevated pressure, in a sealed tube and in the presence or in the absence of an organic solvent.

41. A process as claimed in claim 39 or claim 40, wherein an organic base is present during the reaction as a hydrogen halide acceptor.

42. A process as claimed in any one of claims 39 to 41, wherein the compound of formula (III) is reacted with 2-chloro-4,5-diphenylthiazole or 2-bromo-4,5-diphenylthiazole.

43. A process as claimed in any one of claims 30 to 39, wherein R^1 and R^2 are as defined in claim 2.

44. A process as claimed in claim 30 and substantially as hereinbefore described in any one of Examples 10c or 15 to 18.

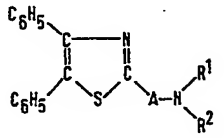
45. A process as claimed in claim 34 and substantially as hereinbefore described in Example 19b.

46. A process as claimed in claim 39 and substantially as hereinbefore described in any one of Examples 1 to 4, 7, 8 or 9.

47. A compound as claimed in claim 1 which has been prepared in a process as claimed in any one of claims 30 to 33 or 44, in a process as claimed in any one of claims 34 to 39 or 45, or in a process as claimed in any one of claims 39 to 42 or 46.

48. A compound as claimed in claim 2 which has been prepared in a process as claimed in claim 43.

49. A compound having the formula



wherein A is as defined in claim 1 and at least one of R^1 and R^2 is C_{1-4} acyl or acyloxyalkyl having from 1 to 4 carbon atoms in the alkyl moiety with the remaining one of R^1 and R^2, if present, being hydrogen, C_{1-4} alkyl or C_{1-4} hydroxyalkyl.

50. A process for preparing a compound as claimed in claim 49, which process comprises reacting a compound as claimed in claim 1, wherein at least one of R^1 and R^2 is hydrogen or C_{1-4} hydroxyalkyl, the remaining one of R^1 and R^2, if present, being hydrogen, C_{1-4} alkyl or C_{1-4} hydroxyalkyl, with an acylating agent.

51. A process as claimed in claim 50 and substantially as hereinbefore described in Example 5 or Example 6.

52. A compound as claimed in claim 49 which has been prepared in a process as claimed in claim 50 or claim 51.

53. A pharmaceutical composition which comprises a compound as claimed in any one of claims 1, 10 to 23, 47, 49 or 52, a salt as claimed in claim 5 or claim 7, a compound or pharmaceutically acceptable salt as claimed in any one of claims 24, 26 or 28, or an N-acylated derivative as claimed in claim 9, and a pharmaceutically acceptable diluent, carrier or excipient.

54. A pharmaceutical composition which comprises a compound as claimed in claim 2 or claim 48, a salt as claimed in claim 6 or claim 8, a compound or pharmaceutically acceptable salt as claimed in any one of claims 25, 27 or 29, or an N-acylated derivative as claimed in claim 9, and a pharmaceutically acceptable diluent, carrier or excipient.

55. A pharmaceutical composition as claimed in claim 53 and substantially as hereinbefore described in Example 20.

56. A method for producing a hypocholesterolemic effect and/or inhibiting platelet aggregation in an animal, which method comprises administering to the animal an effective amount of a compound as claimed in any one of claims 1, 10 to 23, 47, 49 or 52, a salt as claimed in claim 3, claim 5, or claim 7, a compound or salt as claimed in any one of claims 24, 26 or 28, a pharmaceutical composition as claimed in claim 53 or claim 55, or an N-acylated derivative as claimed in claim 9.

57. A method for producing a hypocholesterolemic effect and/or inhibiting platelet aggregation in an animal, which method comprises administering to the animal an effective amount of a compound as claimed in claim 2 or claim 48, a salt as claimed in claim 4, claim 6 or claim 8, a compound or salt as claimed in any one of claims 25, 27 or 29, a pharmaceutical composition as claimed in claim 54, or an N-acylated derivative as claimed in claim 9.

58. A method as claimed in claim 56 and substantially as hereinbefore described.

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